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08/484,786 06/07/95 MACH B MACH-2-CONT.V6

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

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JAMES F HALEY JR
FISH & NEAVE
1251 AVENUE OF THE AMERICAS
NEW YORK NY 10020-1104

EXAMINER
ARTHUR, L

ART UNIT	PAPER NUMBER
1655	26

DATE MAILED: 07/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/484,786	Mach et al.
Examiner	**Group Art Unit**
Lisa Athur	1655

☒ Responsive to communication(s) filed on *Apr 26, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *51-75* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *51-75* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ *is/are objected to by the Examiner.*

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *23*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to the papers filed May 2, 2000. Applicant's have requested a withdrawal of finality under 37 CFR 1.129(A). Currently, claims 51-75 are pending in this application. All of the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance.

MAINTAINED REJECTION

2. Claims 51-72 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons of record. The amendment of May 2, 2000, contains no new arguments and therefore the rejection is maintained for the reasons of record.

In the previous amendment filed November 2, 1998, the response traversed the rejection on the following grounds. The response argues that the skilled artisan could use the instant specification to make the large number of sequences claimed using routine experimentation because the artisan would know that the useful DNA sequences are those that selectively hybridize and that determination of length is routine. The response alleges that once applicants identified the polymorphic and conserved region between DR-BA and DR-B-B, they also "made possible" sequences encoding these regions which specifically hybridize to the regions.

These arguments were deemed non-persuasive because they are allegations which are not supported by the level routine experimentation at the time of filing. As pointed out in the previous office action, in 1983 determination of hybridization conditions that allowed "specific hybridization" between nucleic acids which differed by only a few nucleotides was not routine.

The methods at the time of the invention, such as Connor et al. Used short oligonucleotides (such as 19mers) under very high stringency hybridization conditions to differentiate alleles that differed by only a few nucleotides. The specification only discloses two specific sequences for comparison to detect mismatches for use in making such short oligonucleotides. Furthermore, the specification teaches that under high "criterium" hybridization conditions the inserts of DR-beta-A,B,C and D cross hybridize with one another such that the scope of "specific hybridization" is unclear. Further, the arguments are directed to embodiments to which the claims are not limited. The claims are very broadly drawn to any DNA sequence of any length that can hybridize to some unknown degree of specificity to the specific sequences of the specification. The claims are also drawn to sequences having portions containing any mismatch between these undiscovered hybridizing sequences. The locations, identities and sequences of these mismatch regions are unknown and completely unpredictable in light of the two specific sequences taught in the specification. The specification also does not provide guidance as to how to make sequences which "differ" from the specifically disclosed and the large number of "specifically hybridizing" sequences due to degeneracy of the genetic code. Therefore, this rejection is maintained.

The previous response further traversed the rejection on the following grounds that the specification and the prior art taught how to make oligonucleotides which contained mismatches and how to use those oligonucleotides for HLA typing. All of the arguments and the cited references have been thoroughly reviewed but are deemed non-persuasive for the following reasons. The arguments are convincing that at the time of filing it would have been obvious to try

to find oligonucleotides with the claimed characteristics. However, the specification and prior art do not provide enough specific guidance with regard to mismatches in the DR-B-A,B,C, D alleles and lack of cross reactivity to enable the skilled artisan to reasonably predict what the DNA sequences would be that would be useful for typing. The specification does not describe the structures of these oligonucleotides such that the skilled artisan would be able to reasonably predict what they would be without undue experimentation particularly in 1983. Therefore, for these reasons and the reasons of record, this rejection is maintained.

3. Claims 51-75 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,503,976. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of patent 5,503,976 are drawn to a specific embodiment, i.e. methods and kits using specific 19-mer oligonucleotides, which are encompassed in the more broadly drawn claims of the instant application.

This rejection is maintained pending the filing of a terminal disclaimer.

NEW GROUNDS OF REJECTION

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 51-54are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 51-54,57-69 are broadly drawn to an HLA-DR typing method by hybridization with a DNA seqeunce which codes for a portion of a polypeptide encoded by DR-beta-A, DR-beta-B or DR-beta-C wherein the portion comprises a region of mismatch or a sequence which hybridizes to this sequence or to DR-beta-A, DR-beta-B or DR-beta-C. Claims 53 and 54 are broadly drawn to an HLA-DR typing method by hybridizing a DNA sample with a sequence that can hybridize to a polymorphic region of an HLA-DR-beta chain locus wherein the seqeunce encodes amino acids 8-14,26-32 and 72-78. Claims 57-58 are broadly drawn to an HLA-DR typing method in which sample DNA is hybridized to a DNA sequence encoding "a majority" of the region defined by amino acids 8-14,26-32,39-45 or 72-78 of a polypeptide encoded by DR-beta-A, DR-beta-B or DR-beta-C or allelic variants. Claims 59-65 are dependent upon these claims. Claim 66 is broadly drawn to an HLA-DR typing kit including a DNA sequence which codes for a portion of a polypeptide encoded by DR-beta-A, DR-beta-B or DR-beta-C wherein the portion comprises a region of mismatch or a sequence which hybridizes to this sequence or to DR-beta-A, DR-beta-B or DR-beta-C. Claims 67 is drawn to a kit containing a sequence that

can hybridize to a polymorphic region of an HLA-DR-beta chain locus wherein the seqeunce encodes amino acids 8-14,26-32 and 72-78. Claims 73 is broadly drawn to a DNA sequence which hybridizes to a polymorphic region a sequence that can hybridize to a polymorphic region of an HLA-DR-beta chain locus wherein the seqeunce encodes amino acids 8-14,26-32 and 72-78. wherein the polymorphic region is encoded by amino acids 8-14,26-32,72-78, portions of any of these sequence and allelic variants of any of these sequences. Claim 74 is drawn to DNA sequences encoding polymorphic regions of an HLA-DR-beta chain locus wherein the seqeunce encodes amino acids 8-14,26-32 and 72-78. Claim 75 is drawn to DNA sequences encoding a majority of the region of amino acids 8-14,26-32 and 72-78 of DR-beta-A, DR-beta-B or DR-beta-C or allelic variants or complementary sequences.

The specification has described polynucleotides consisting of DR-beta-A, -B-and C and describe the regions within the polypeptide encoded by these polynucleotides, i.e. amino acids 8-14, 24-32 and 72-78 which are variable between -A, -B and -C and a region which is conserved between -A, -B and -C, i.e. amino acids 38-45 and describes methods of using these polynucleotides for HLA-DR typing. However, the claims, as written, encompass polynucleotides and methods of using polynucleotides that vary substantially in length and also in nucleotide composition. Specifically, in claims 51 and 52 the typing method encompasses using DNA sequences that only code for a portion of a polypeptide encoded by DR-beta-A, -B-and C wherein the portion is a region of mismatch. Consequently, the DNA seqeunce used in the method can be any sequence which is different from DR-beta-A, -B or -C. Since the specification

has only described three specific DR-beta sequences and because the genus of sequences encompassed by the recitation in the claims is enormous with no common structural feature, the three species described in the specification are not representative of the genus. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable the skilled artisan to identify the DNA sequences encompassed for use in the method.

Claims 53 and 54 also encompass a genus of typing methods for which a representative number of species have not been described. Specifically, claims 53 and 54 encompass typing methods in which DNA minimally encoding amino acids 8-14, 26-32 or 72-78 of any HLA-DR-beta chain is used to determine one or more HLA alleles. However, the specification has only described three specific DR-beta chain coding sequences. Because of the polymorphic nature of these genes, there may by many different DR-beta chain sequences of which three is not representative. Furthermore, the claims, as written encompass using genomic sequences as well as the cDNA sequences but the genomic DNA sequence has not been described in the specification to establish that applicant was in possession of genomic sequences at the time of filing. Additionally, the claims are drawn to method using DNA sequences which are capable of hybridizing to polymorphic sequences which makes the genus of DNA sequences which can be used in the method even larger. Sequences identified by hybridization would not predictably have the same structural and functional characteristics as the disclosed species because there is no way to determine what variations would be tolerated without making the method inoperable as a typing method.

Claims 57-65 and 70-71 are not supported by the description in the specification because the claims encompass typing method using a DNA sequence which minimally, encodes "a majority" of a region of amino acids 8-14, 26-32, 39-45 or 72-78 of HLA-DR-beta -A, -B, -C or allelic variants. The DNA sequences used in the claim methods include a very large genus of sequences including genomic sequences, coding sequences for DR-beta chains different from those described in the sequence as well as sequences which do not encode DR-beta chains as a result of the vague language used in (a) of claim 57 and © of claim 58. The claims are not limited to the DNA sequences consisting of the specifically described regions of amino acids 8-14, 26-32, 39-45 and 72-78 of DR-beta, A, -B and -C of this application, but instead encompass large DNA sequences which only contain a few of the amino acids from these regions. The DNA seqeunce is not even limited to coding for the same amino acids as in the described regions because the claims recite that DNA encodes a majority of the region defined by amino acids .... This statement is not the same as saying that the DNA encodes a majority of the amino acid sequence in the region of amino acids .... of nucleic acid X. Consequently, the claims are broadly drawn to a huge number of different typing methods using completely different probes when only three specific DR-beta chain sequences have been described. These three seqeunce do not constitute a representative number of species of the genus due the high degree of variability in the structures and functions of the DNAs encompassed by the genus and the lack of a common structural feature of the elements of the genus.

Claims 66-69 and 72 are drawn to typing kits that contain the same genuses of DNA sequences as claimed in the typing methods discussed above and lack sufficient description for the same reasons as given above. Additionally, newly added claims 73-75 drawn to isolated DNA sequences encompass a huge genus of DNA sequences which have not been supported by the description of a representative number of species for the same reasons as discussed above.

Thus, the written description of the instant specification only provides support for a typing method using the polynucleotides of DR-beta-A, B or -C or polynucleotides consisting of the specifically described polymorphic regions of DR-beta-A, B or -C and the specifically described conserved region, i.e. the method for which a patent was granted in patent 5,503,976. However, the full breadth of the claims to not meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Application under the 35USC112, first paragraph"written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday, December 21, 1999.

Claims 51,53,55,57,59,60,62,64,70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an HLA-DR typing method comprising restricting DNA, size fractionating the restricted DNA and then hybridizing the specifically recited sequences, does not reasonably provide enablement for an HLA-DR typing method comprising

hybridizing DNA in a sample with the specifically recited sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are not commensurate in scope with the disclosure because the specification does not provide sufficient guidance to enable the skilled artisan to make and use the claimed invention without undue experimentation. The claims broadly encompass typing methods wherein DNA from a sample is hybridized to a probe for an HLA-DR beta chain sequence including dot blots and solution hybridizations and other procedures which do not require restriction digestion and size fractionation. However, the specification teaches that the disclosed DR-beta-A, B and C sequences detected DR beta chain alleles after restriction digestion and size fractionation and that typing was performed by distinguishing the hybridization pattern in one sample from another. Since all individuals have a DR beta chain locus and since the specification teaches that sequences from the different loci cross hybridize, a hybridization assay which did not generate a fractionated restriction pattern would not distinguish individuals since the DR-beta-A, B and C sequences would be expected to cross hybridize to moist samples. That is, the detection of hybridization does not appear to be useful for typing, but instead the pattern of hybridization using the different disclosed probes. Therefore, the skilled artisan would be required to practice undue experimentation in order to perform an HLA typing method by merely hybridizing in a sample without a prior fractionation step.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 51-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 51, 52,60-66,68 are indefinite over the recitation of "the expressed portion of the DNA sequence of DNA insert DR-beta-A, DR-beta-B or DR-beta-C" because this phrase make the claims unclear as to metes and bounds of "the DNA seqeunce". The specification teaches that the DNA of insert DR-beta-A, DR-beta-B or DR-beta-C was cDNA obtained from mRNA. Consequently, the entire sequence of the inserts would be presumed to be "the expressed portion". As written the phrase implies that the inserts contain an expressed and a non-expressed portion which is in conflict with the teachings in the specification.

B) Claims 57, 59,60,62, 64 and 75 are indefinite over the recitation of "encoding a majority of the region..." Because as written the claims are unclear as to what would be encompassed by "a majority", at least 50%, 51% and greater, or more that 51%, for example.

C) Claim 59 is indefinite over the recitation of "said second DNA" because this term lacks antecedent basis in claim 57 which recites "said DNA sequence".

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims are rejected under 35 U.S.C. 102(b) as being anticipated by Larhammar et al. Larhammer et al. teach an isolated DNA sequence which encodes the complete amino acid sequence of an HLA-DR antigen beta chain (see Figure 2). The DNA of Larhammer et al. hybridizes to an HLA-DR-beta chain locus since it is the coding sequence of the locus and is able to hybridize to a polymorphic region of the locus to allow determination of an HLA allele wherein the polymorphic region encodes amino acids 8-14, 26-32 or 72-78 or a portion of these regions because the DNA sequence of Larhammer et al. Hybridizes to the entire coding sequence which includes the recited region. Larhammer et al. Teaches the DNA sequence of claim 75 because the claim as written does not limit the DNA to a sequence which is exactly that of amino acids 8-14, 26-32, 39-45 or 72-78 of the DNA of DR-beta-A, -B, or -C but instead is broadly drawn to DNA sequences which encode a majority of a region defined by amino acids 8-14 ....or 72-78 of the polypeptide coded for by DR-beta-A, -B, or -C. As written the DNA seqeunce is not limited to even containing some of the amino acids from the disclosed sequences but instead encompasses the equivalent region , i.e. DNAs encoding the same amino acid positions but of different sequence. Furthermore, the region at 72-78 is a conserved region in the DR-beta-chains which

would be expected to be present in the DNA of Larhammer et al. Additionally, the claim is drawn to "allelic variants" in which the Larhammer et al. DNA seqeunce is encompassed.

4. No claims are allowable.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday from 7:00 am to 3:30 pm and on Tuesday-Wednesday from 7:00 am -1:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600

July 17, 2000